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(21) International Application Number: PCT/CA98/00764 (22) International Filing Date: 10 August 1998 (10.08.98) (30) Priority Data: 60/055,247 11 August 1997 (11.08.97) US (71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100 Cunard, Laval, Québec H7S 2G5 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): LLINAS-BRUNET, Montse [CA/CA]; 10543 Bélair, Pierrefonds, Québec H2V 2W8 (CA). BAILEY, Murray, Douglas [CA/CA]; 344 Groulx, Pierrefonds, Québec H8Y 1B3 (CA). HALMOS, Teddy [CA/CA]; 1935 Jean Ricard #8, Laval, Québec H7T 2K4 (CA). POUPART, Marc-André [CA/CA]; 101 Aimé Séguin, Laval, Vimont, Québec H7M 1B3 (CA). TSANTRIZOS, Youla [-/-]; 1590 Champigny, Saint-Laurent, Québec H4L 4P7 (CA). (74) Agent: VAN ZANT, Joan, M.; Van Zant & Associates, Suite 1407, 77 Bloor Street West, Toronto, Ontario M5S 1M2 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.
(54) Title: HEPATITIS C INHIBITOR PEPTIDE ANALOGUES <div style="text-align: center; margin: 20px 0;"> <p>P6 P5 P4 P3 P2 P1</p> <p>(I)</p> </div> <p>(57) Abstract</p> <p>Compound of formula (I) active against the Hepatitis C virus, wherein B is an acyl derivative; a is 0 or 1; R₆, when present, is carboxy(lower)alkyl; b is 0 or 1; R₅, when present, is C₁₋₆ alkyl, or carboxy(lower)alkyl; Y is H or C₁₋₆ alkyl; R₄ is C₁₋₁₀ alkyl; R₃ is C₁₋₁₀ alkyl; W is -NH-CH(R₂)-C(O)-, wherein R₂ is C₁₋₆ alkyl; C₆ or C₁₀ aryl; C₇₋₁₆ aralkyl; or carboxy(lower)alkyl; or W is a proline derivative; Q is a group of the formula -Z(R₁)-C(O)-R₁₃, wherein Z is CH or N; R₁ is C₁₋₆ alkyl or C₁₋₆ alkenyl both optionally substituted with thio or halo; and R₁₃ is an activated carbonyl substituent, or Q is a phosphonate group of the formula -CH(R₁)-P(O)R₁₅R₁₆ wherein R₁₅ and R₁₆ are independently C₆₋₂₀ aryloxy; and R₁ is as defined above.</p>		

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After 60 min pre-incubation at 30°C, 20 µL of substrate solution (50 mM Tris-HCl, pH 8, 0.5 M Na₂SO₄, 50 mM NaCl, 0.1 mM EDTA, 665 µM Succ-AAA-pNA) were added to each well and the reaction was further
5 incubated at 30°C for 60 min after which time the absorbance was read on the UV Thermomax® plate reader. Rows of wells were allocated for controls (no inhibitor) and for blanks (no inhibitor and no enzyme).

10

The sequential 2-fold dilutions of the inhibitor solution were performed on a separate plate by the liquid handler using 50 mM Tris-HCl pH 8, 50 mM NaCl, 0.1 mM EDTA, 0.02% Tween-20, 15% DMSO. All other
15 specificity assays were performed in a similar fashion.

The percentage of inhibition was calculated using the formula:

20

$$[1 - ((UV_{inh} - UV_{blank}) / (UV_{ctl} - UV_{blank}))] \times 100$$

A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (IC₅₀) was calculated by
25 the use of SAS software (Statistical Software System; SAS Institute, Inc., Cary, N.C.).

Example 21

Tables of compounds

30

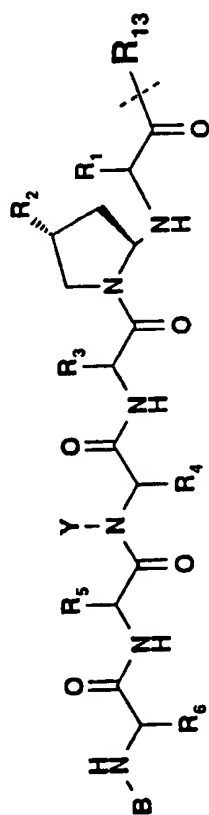
The following tables list IC₅₀ values of compounds representative of the invention.

The following abbreviations are used:

- IC₅₀**: The concentration required to obtain 50% inhibition in the NS3 protease/NS4A cofactor peptide radiometric assay according to Example 19.
- 5 **HLE**: The concentration required to obtain 50% inhibition in the human leukocyte elastase assay;
- PPE**: The concentration required to obtain 50% inhibition in the porcine pancreatic elastase assay;
- 10 **Other**: Figures unmarked indicate the concentration required to obtain 50% inhibition in the bovine pancreatic α -chymotrypsin assay; figures marked with ** indicate the concentration required to obtain 50% inhibition in the human liver cathepsin B assay; **MS**: Mass spectrometric data (MH⁺ from FAB); **AAA**: amino acid analysis data expressed in % peptide recovery;
- 15 **Acpr**: 1-amino-cyclopropylcarboxylic acid; **Acpe**: 1-amino-cyclopentylcarboxylic acid; **Abu**: aminobutyric acid; **Chg**: cyclohexylglycine (2-amino-2-cyclohexyl-acetic acid); **Hyp**: 4(R)-hydroxyproline; **Hyp(4-Bn)**: 4(R)-benzyloxyproline; **Pip**: pipecolic acid; **Tbg**: tert-butylglycine; **Ac**: acetyl; **Bn**: benzyl; **O-Bn**: benzyloxy; **DAD**: 3-carboxypropionyl; and **DAE**: 4-carboxybutyryl.

Table 1

P6 P5 P4 P3 P2 P1



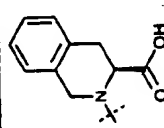
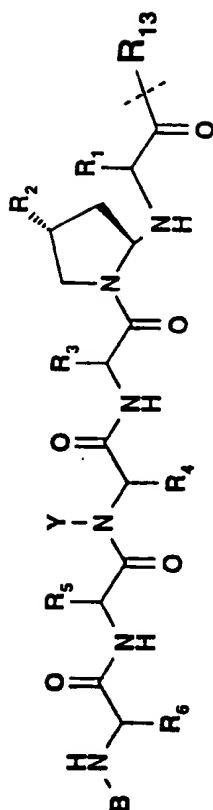
cpd	B	P6	P5	P4	P3	R ₂	R ₁	R ₁₃	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH ⁺)	AAA (%)
101	Ac	Asp	D-Glu	Ile	Val	O-Bn	ethyl	CF ₃	9.4	<1.2			857.4	
102	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	CF ₃ CF ₃	0.21				921	99.2
103	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	C(O)NH-Bn	0.023				936	
104	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	H	0.14	7	8	8	803	115
105	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	NH ₂	54				818	108
106	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	CH ₂ CH ₂ -Ph	5.4	16			908	107.8
107	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	NHCH ₂ Ph	3				908	100.8
108	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	(S)-NH-CH(Me)Ph	0.71	3	>300	>300	922	107
109	Ac	---	---	Chg	Val	O-Bn	propyl	C(O)-NH-Bn	23	2			718.3	
110	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl		8				(MH ⁺) 753.5	

Table 1

P6 P5 P4 P3 P2 P1



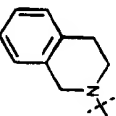
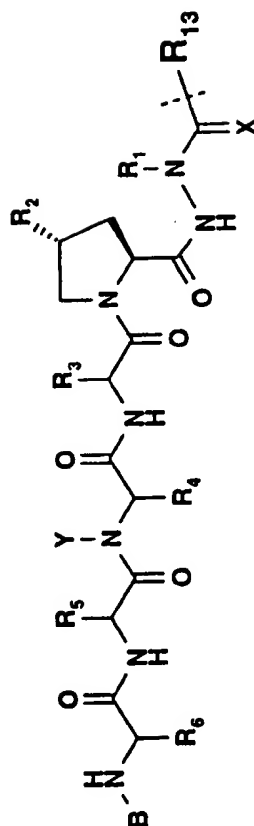
cpd	B	P6	P5	P4	P3	R ₂	R ₁	R ₁₃	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH ⁺)	AAA (%)
111	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl		20					
112	Ac	Asp	D-Glu	Ile	Val	H	propyl	C(O)-NH-Bn	2	0.03	<0.06	10.3	814.4	104.4
113	Ac	Asp	D-Glu	Ile	Val	H	propyl	CF ₂ -CF ₃	12.8	0.07	<0.06	18		
114	Ac	Asp	D-Glu	Ile	Val	H	propyl	CF ₃	23.5	0.05	0.2	4.4	749.3	106.7
115	Ac	Asp	D-Glu	Ile	Val	H	propyl	C(O)-NH-Bn	0.66	0.11	<0.06	30	814	99.4
116	Ac	---	---	Chg	Val	O-Bn	propyl	C(O)-NH-CH ₂ -4-pyridine	25					

Table 2

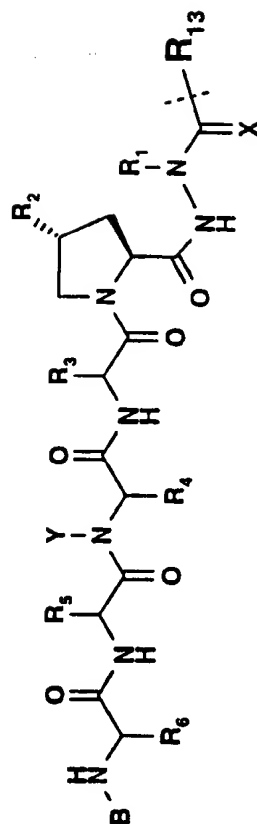
P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R2	R1	X	R13	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	MS (MH ⁺)	AAA (%)
201	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	NHCH ₂ -C(O)OEt	3.9	27.4	168	905.2	
202	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	CH ₂ CH ₂ -Ph	0.63	5.5		908.4	
203	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	NHCH ₂ -Ph	0.59			909.6	
204	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	(R)-NH-CH(Me)Ph	4.2			923.6	
205	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	(S)-NH-CH(Me)Ph	0.078	5.1	4.1	923.6	93.4
206	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	OCH ₂ Ph	0.79	<0.6	<0.6	910	95.6
207	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	NHCH ₂ -C(O)OH	3.75			877.1	106.5
208	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	CH ₃	14.5			818.2	101.9
209	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	NH ₂	20.5			819.3	100.6
210	Ac	Asp	D-Glu	Ile	Val	O-Bn	Butyl	O	(S)-NH-CH(Me)Ph	0.085	4		937.5	95.4
211	Ac	Asp	D-Glu	Ile	Val	O-Bn	Butyl	O	NH ₂	47			833	84

Table 2

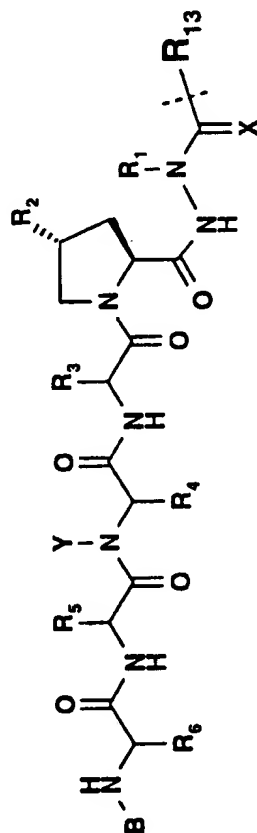
P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R2	R1	X	R13	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	MS (MH ⁺)	AAA (%)
212	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	(S)-NH-CH(Me)-naphthyl	0.58	0.4		974.3	98.9
213	Ac	Asp	D-Glu	Ile	Val	O-Bn	Ethyl	O	(S)-NH-CH(Me)-Ph	0.079	36		909.9	103.3
214	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	(S)-NH-CH(Et)-Ph	0.44			937.5	
215	Ac	---	---	Chg	Val	O-Bn	Propyl	O	(S)-NH-CH(Me)-Ph	45	5		705.5	95.8
216	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	(R)-CH(OH)-Ph	9.6			(MH) 908.5	
217	Ac	Asp	D-Glu	Ile	Val	H	propyl	O	(S)-NH-CH(Me)-Ph	1.04			803.4	93.2
218	Ac	Asp	D-Glu	Ile	Val	O-Bn	isopentyl	O	(S)-NH-CH(Me)-Ph	3.3			951.5	99.5
219	Ac	Asp	D-Glu	Ile	Val	O-Bn	pentyl	O	(S)-NH-CH(Me)-Ph	0.43	151		951.5	
220	HOOC (CH ₂) ₂ -C(O)	---	D-Asp	Ile	Val	H	propyl	O	(S)-NH-CH(Me)-Ph	6.9			(MH) 744.5	97.5
221	Ac	Asp	D-Glu	Ile	Val	O-Bn	Me	O	(S)-NH-CH(Me)-Ph	0.52	168		895	94
222	Ac	Asp	D-Glu	Ile	Val	O-Bn	(CH ₂) ₂ -isopropyl	O	(S)-NH-CH(Me)-Ph	8.9	>300		951.4	98.2
223	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	N(CH ₃)-Bn	11			923.5	105.5
224	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	S	NH-Bn	5			(MH)	

Table 2

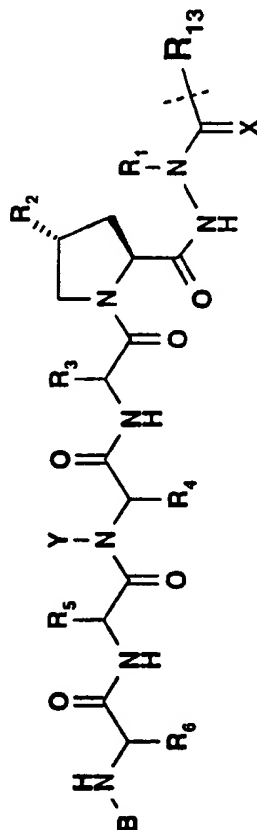
P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R2	R1	X	R13	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	MS (MH ⁺)	AAA (%)
225	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	COCH ₃	13			923.4	
226	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		6.3			862.3	102.3
227	Ac	---	---	Chg	Val	O-Bn	propyl	O	COOH	39.5			(MH ⁺) 628.3	
228	Ac	Asp	D-Glu	Ile	Val	O-Bn	CH ₂ -CF ₃	O	(S)-NH-CH(Me)Ph	0.63			(MH ⁺) 961.4	
229	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		0.13	3.1		(MH ⁺) 933.4	94.1
230	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	(S)-NH-CH(Me)	0.36			929.5	100.6
231	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		0.5			953.4	107.3

Table 2

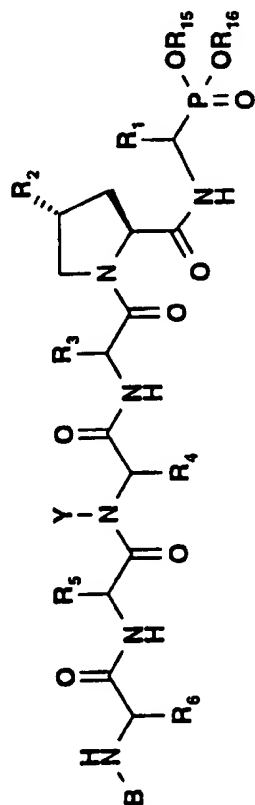
P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	P2	P1	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	MS (MH ⁺)	AAA (%)
232	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	3.2			977.4	96.9
233	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	1.5			(MH) 913.5	
234	Ac	Asp	D-Glu	Ile	Val	O-Bn	CH ₂ =CH- N-benzyl	3.7			907.5	

Table 3

P6 P5 P4 P3 P2 P1

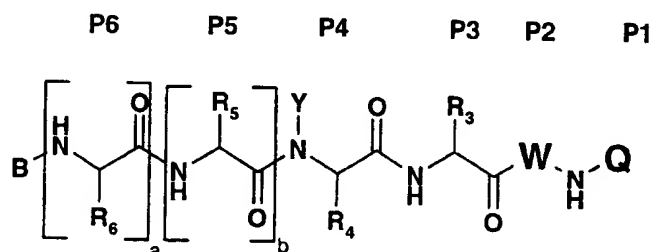


entry #	B	P6	P5	P4	P3	R ₂	R ₁	R ₁₅	R ₁₆	IC ₅₀ (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH ⁺)	AAA (%)
301	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O-Ph	O-Ph	0.029	<0.6	<0.6	3 >300	1007	86.6
302	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O-Ph	O-Ph	26				1007	

What is claimed is:

1. A compound of formula I:

5



(I)

wherein B is an acyl derivative of formula $R_{11}-C(O)-$
 wherein R_{11} is C_{1-10} alkyl optionally substituted with
 10 carboxyl; or R_{11} is C_6 or C_{10} aryl or C_{7-16} aralkyl
 optionally substituted with a C_{1-6} alkyl;

a is 0 or 1;

R_6 , when present, is carboxy(lower)alkyl;

b is 0 or 1;

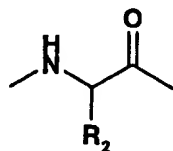
15 R_5 , when present, is C_{1-6} alkyl, or
 carboxy(lower)alkyl;

Y is H or C_{1-6} alkyl;

R_4 is C_{1-10} alkyl; C_{3-10} cycloalkyl;

R_3 is C_{1-10} alkyl; C_{3-10} cycloalkyl;

20 W is a group of formula II:



Formula II

wherein R_2 is C_{1-10} alkyl or C_{3-7} cycloalkyl optionally
 25 substituted with carboxyl; C_6 or C_{10} aryl; or C_{7-16}
 aralkyl; or